Epidemiology of Rotavirus Infection and the Need for a Vaccine in Asia

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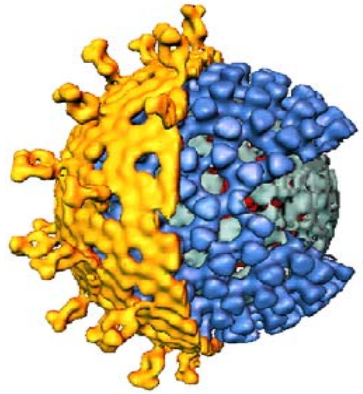
Outline

- Epidemiology & global disease burden
- Asian Rotavirus Surveillance Network
- RV disease burden in Asia
- RV economic burden & cost-effectiveness
- Prospects for vaccine introduction

Rotavirus Strains



- Serotyping based on 2 structural proteins (G & P)
  - ~ 10 possible "G" serotypes (1, 2, 3, 4, 9)
  - ~ 11 possible "P" serotypes (4, 8)
- Strains vary:
  - By region
  - Over time
- Knowledge of strains important for vaccine development

Clinical presentation of Rotavirus

- Acute watery diarrhoea - self-limiting, usually 3-8 days, possibly longer
- Fever - first few days - can be high
- Vomiting - first few days

Compared to other common causes of diarrhoea - *more severe with greater risk of dehydration & hospitalisation*

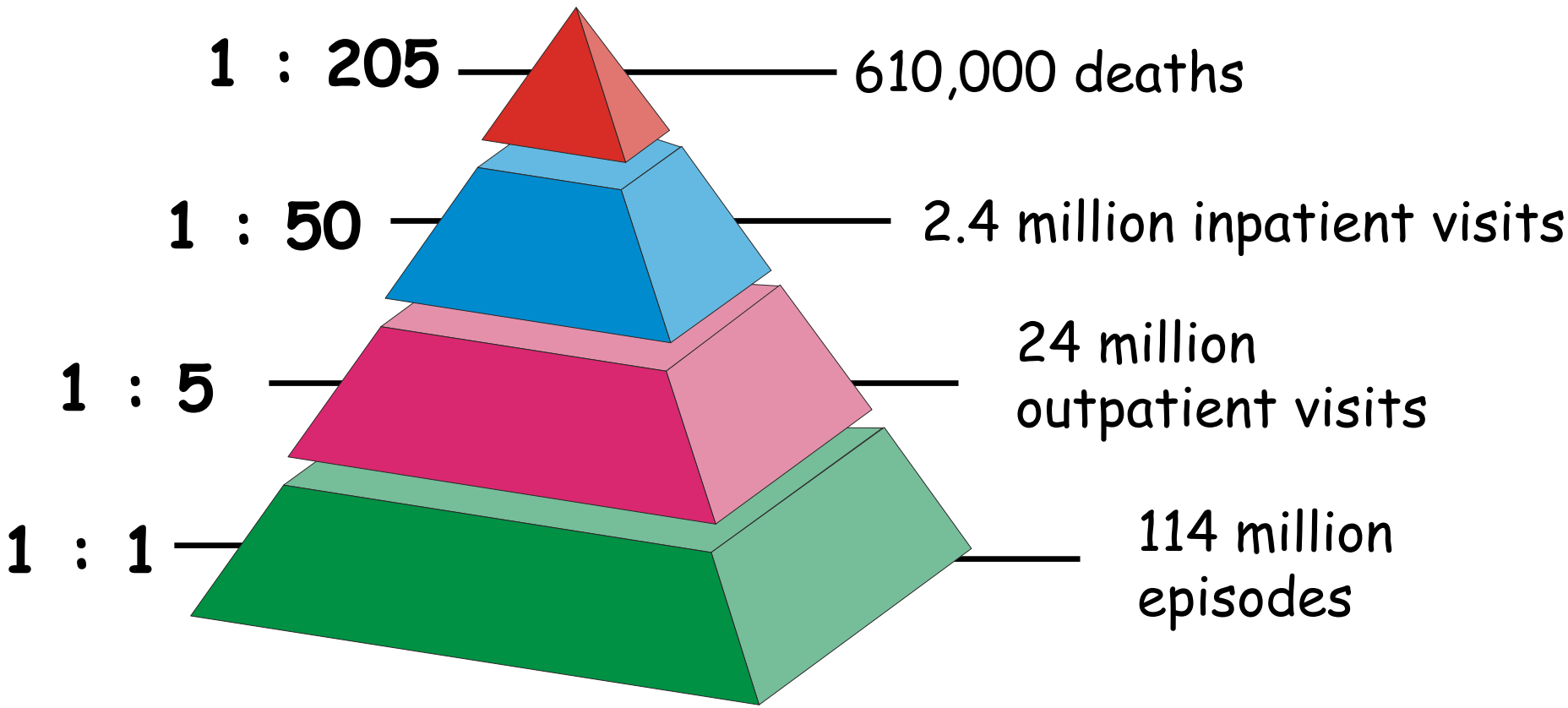
Rotavirus Epidemiology

- A disease of young children
  - Peak symptomatic disease 6-24 months
  - Uncommon or asymptomatic <3 months
  - Virtually all children infected and ill
- A problem in both developed and developing countries

Differences in Rotavirus Epidemiology between Countries

	Developing	Developed
Peak age (mo)	6–9	9–15
Strains	diverse	4–5
Co-infections	common	uncommon
Co-morbidity	malnutrition	uncommon
Mortality	high	low

Global Rotavirus Disease Burden



Glass *et al. Lancet* 2006;368:323-332
Parashar *et al. Emerg Inf Dis* 2006;12:304-6

Rotavirus Mortality by Income

Income group	Births (Millions)	Diarrhoea deaths	% RV	Risk of dying from RV <5yrs
Low	70	1,805,000	20	1 in 205
Low-mid	37	274,000	25	1 in 542
High-mid	12	33,000	31	1 in 1152
High	10	<1000	34	1 in 48,680
Total	129	2.1 M	-	**1 in 293**

Parashar *et al. Emerg Inf Dis* 2003

Mortality & Morbidity

- Mortality

  Predominantly developing countries

  - One quarter of diarrhoea deaths globally
  - ~ 610,000 per year
- Morbidity

  Both developed & developing countries

  - 30-50% of diarrhoea admissions
  - 10-15% community diarrhoea

How best to control rotavirus?

- Disease not prevented by good sanitation & hygiene
- Despite potential for ORS, IV fluids often needed for severe disease
- International authorities (WHO, Institutes for Medicine, GAVI) highlight need for rotavirus vaccines

CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

March 19, 1999 / Vol. 48 / No. RR-2

MMWR™
MORBIDITY AND MORTALITY WEEKLY REPORT

Recommendations and Reports

Rotashield®

Rotavirus Vaccine for the Prevention of Rotavirus Gastroenteritis Among Children

RECOMMENDATIONS FOR THE USE OF ROTAVIRUS VACCINE

Routine Administration

Routine immunization with three oral doses of RRV-TV is recommended for infants at ages 2, 4, and 6 months. Because natural rotavirus infections occur early in

1st ARSN Meeting
Bangkok
Feb 1999

Messages

- Rotavirus vaccine now available in US
- Decision makers will need local disease burden data
- What data do we have?
- What data do we need?

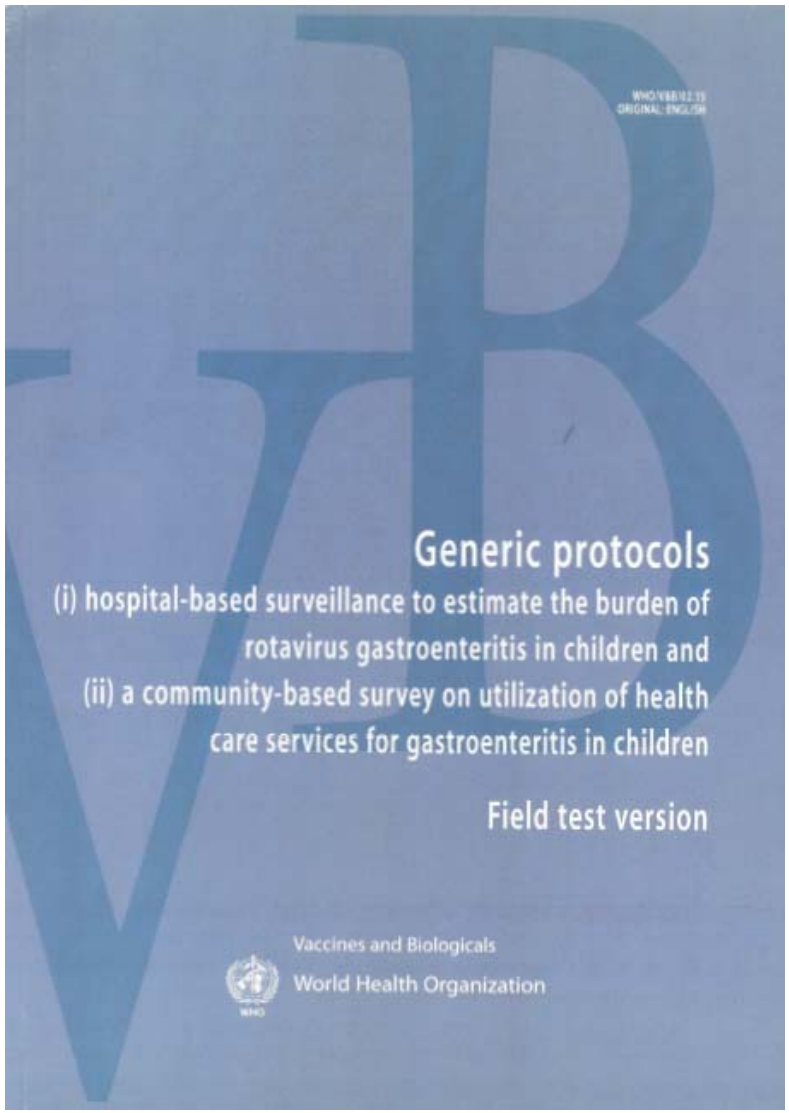
Awareness of rotavirus disease burden ?

- Diarrhoea recognised as leading cause of morbidity and mortality BUT *most doctors & policy makers often don't appreciate importance of rotavirus*
- Aetiology does not usually alter management – thus diagnosis of rotavirus often not made
- Policy makers may think improving water and sanitation may prevent rotavirus - incorrect

GAVI Task Force on R&D recommended:

- Simple generic surveillance protocols be developed
- Regional surveillance networks be established

WHO's Generic Protocol



- ✓ Hospital-based surveillance
- ✓ Simple data collection
- ✓ Outcomes:
  - rates of diarrhoea hospitalisations
  - and/or % RV positive
- ✓ Strain characterisation

CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

July 16, 1999 / Vol. 48 / No. 27

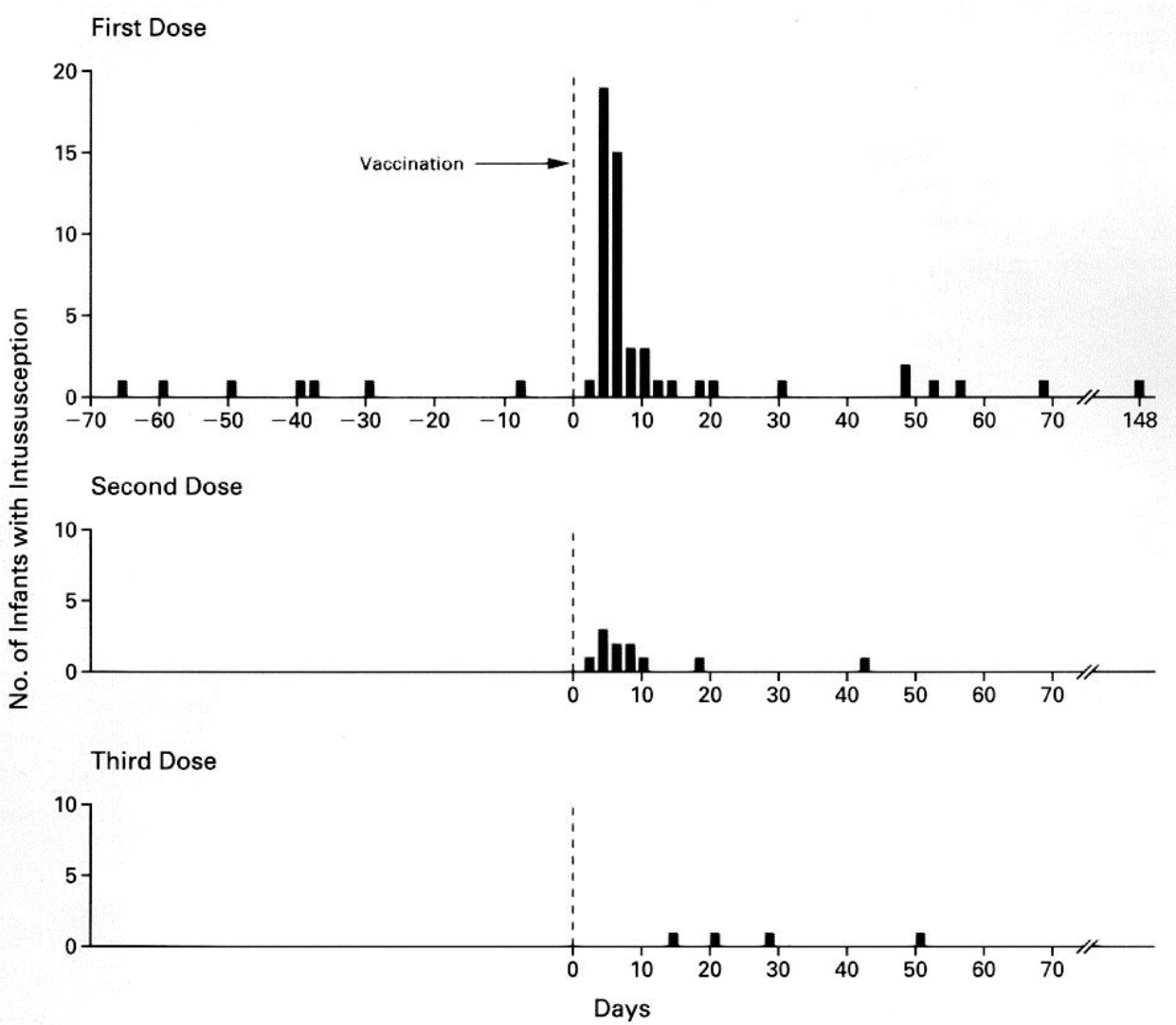
MMWR™
MORBIDITY AND MORTALITY
WEEKLY REPORT

Intussusception Among Recipients of Rotavirus Vaccine — United States, 1998–1999

On August 31, 1998, a tetravalent rhesus-based rotavirus vaccine (RotaShield®*, Wyeth Laboratories, Inc., Marietta, Pennsylvania) (RRV-TV) was licensed in the United States for vaccination of infants. The Advisory Committee on Immunization Practices (ACIP), the American Academy of Pediatrics, and the American Academy of Family Physicians have recommended routine use of RRV-TV for vaccination of healthy infants (*1,2*). During September 1, 1998–July 7, 1999, 15 cases of intussusception (a bowel obstruction in which one segment of bowel becomes enfolded within another segment) among infants who had received RRV-TV were reported to the Vaccine Adverse Event Reporting System (VAERS). This report summarizes the clinical and epidemiologic features of these cases and preliminary data from ongoing studies of intussusception and rotavirus vaccine.

VAERS

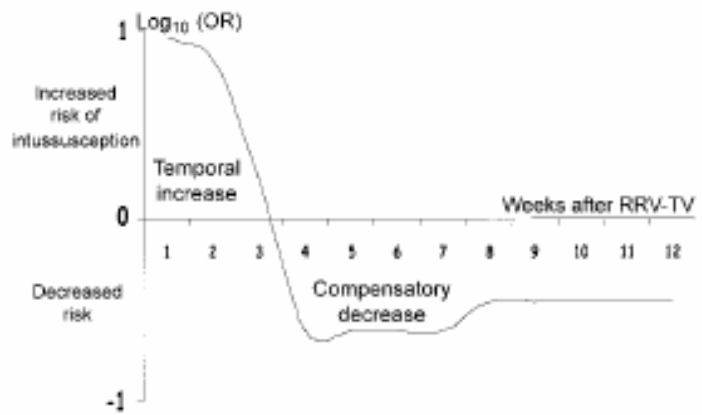
RRV-TV & IS temporal association



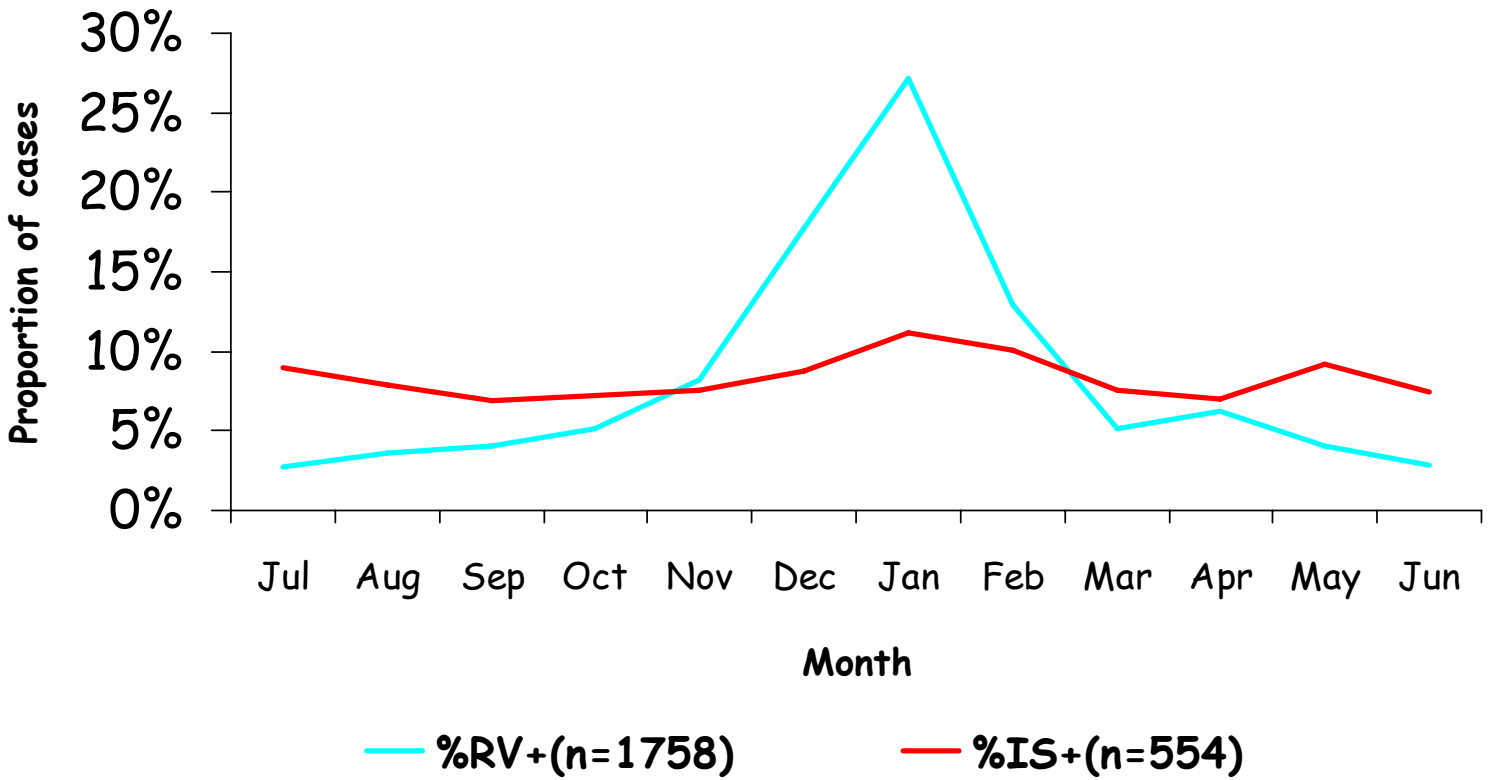
Murphy. New Engl J Med 2001;344: 564

Withdrawal of Rotashield®

- Associated with intussusception
- Withdrawn in 1999
- Risk of intussusception
  - highest 3-10 days post-vaccination
  - ~ 1 in 10,000
  - ? less or non-existent
  - ? Age related



Will intussusception occur with other rotavirus vaccines?



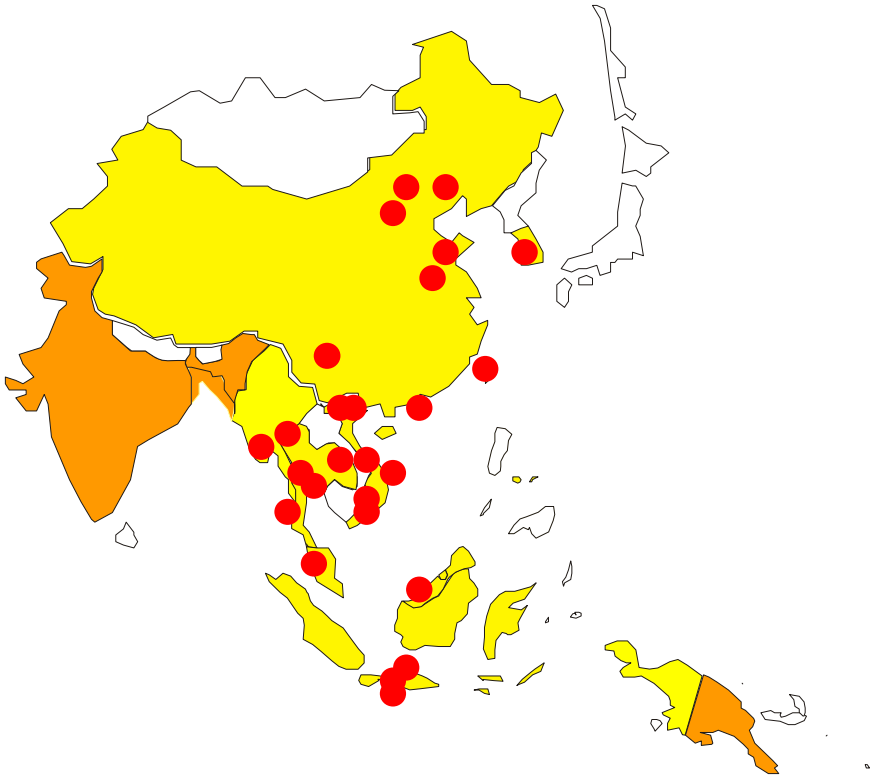
Hong Kong : Intussusception (Jul 1997-Jun 2003) & Rotavirus (Apr 2001-Mar 2003)

Out of CRISIS Comes OPPORTUNITY

- Reinvigorating the competition
  - Big pharma (GSK, Merck)
  - Local producers (China/India)
- Parallel testing in both developed & developing countries
- Increasing awareness of the potential for rotavirus vaccines

Glass. Lancet 2004;363:1547

The Asian Rotavirus Surveillance Network: Phase 1



GAVI eligible

- ✓ China
- ✓ Hong Kong
- ✓ Indonesia
- ✓ Malaysia
- ✓ Myanmar
- ✓ South Korea
- ✓ Taiwan
- ✓ Thailand
- ✓ Vietnam

2nd Workshop of ARSN

Bangkok, May 2002

Publication of 1st year results

- August 2001 to July 2002
- South Korea started in June 2002
- 33 hospital in 8 countries
- Data of 16,000 hospitalisations for diarrhoea during 1st year
- Data collation by CDC

Bresee. Emerg Infect Dis. 2004;10:988

Stools Tested

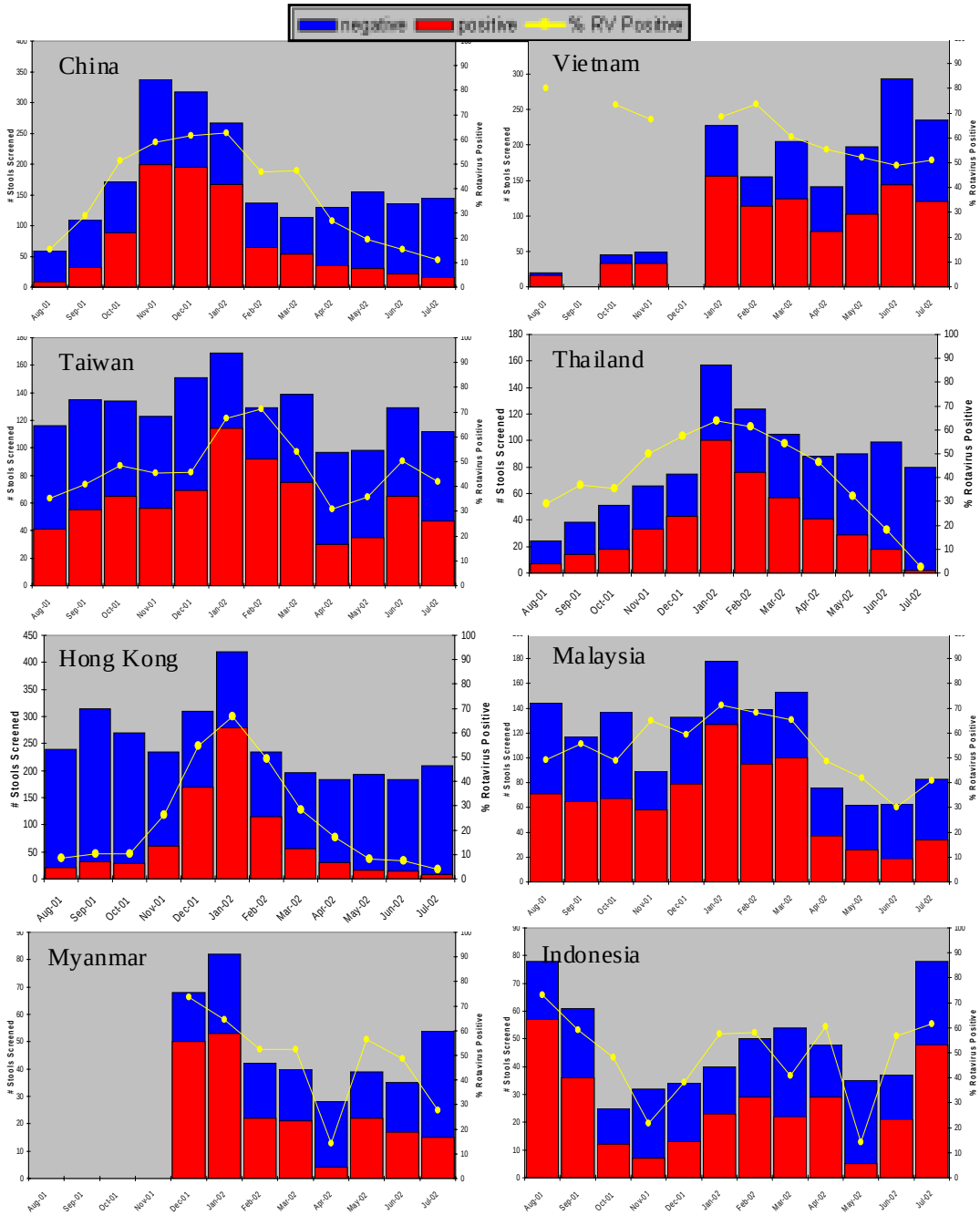
- 11,498 stools from 16,1173 patients = 71%
- **45%** of tested specimens positive for rotavirus

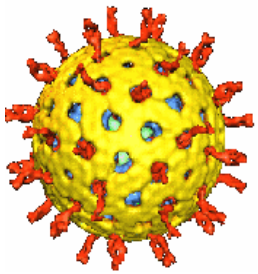
Rates of Rotavirus Detection

Aug 2001–Jul 2002

Sites	Tested	RV+ %	Range
China	2079	44	24-65
Taiwan	1532	49	43-53
Hong Kong	2986	28	18-35
Vietnam	1570	59	47-67
Myanmar	388	53	53
Thailand	992	44	38-49
Malaysia	1374	57	52-59
Indonesia	577	52	47-57
Overall	11,498	45	18-67

Figure 1. Seasonality of rotavirus in member countries of the Asian Rotavirus Surveillance Network





4th Workshop of the Members of the Asian Rotavirus Surveillance Network

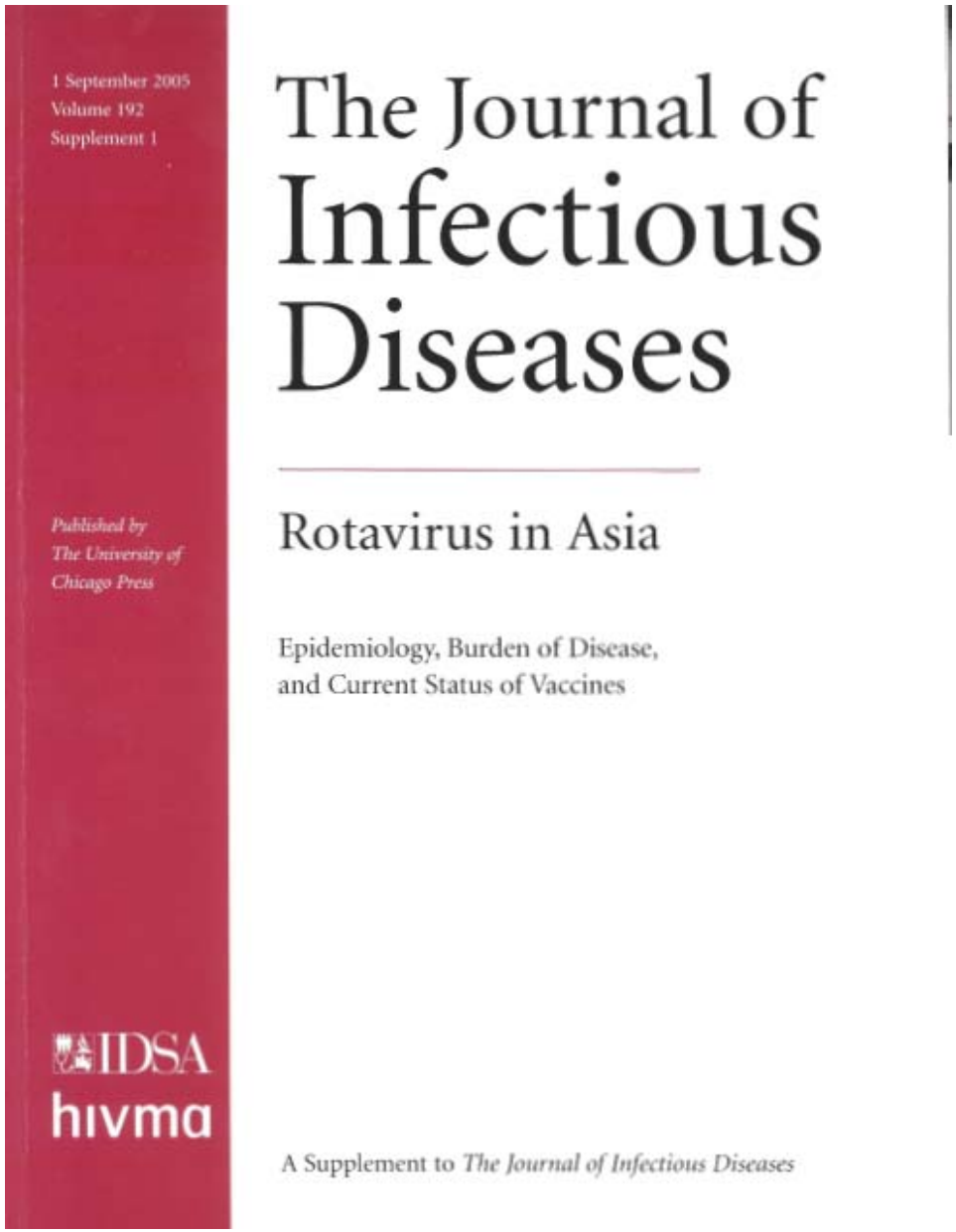
Manila, Philippines

21-22 October 2003

2nd Phase ARSN launched 2003

- ✓Bangladesh (2)
- ✓Cambodia (1)
- ✓Kyrgyzstan (2)
- ✓Lao PDR (1)
- ✓Mongolia (2)
- ✓Nepal (1)
- ✓Pakistan (2)
- ✓Philippines (7)
- ✓Sri Lanka (1)
- ✓Uzbekistan (2)
- ✓China (8)
- ✓Indonesia (5)
- ✓Myanmar (1)
- ✓Thailand (2)

GAVI eligible



Sep 2005

- Disease Burden : Taiwan, Korea, Hong Kong, Malaysia, Thailand, China, Japan, Myanmar, India, Vietnam
- Economic Burden : HK & Japan, cost-effectiveness projections for Asia
- Vaccine updates : RIX4414, Pentavalent & Hexavalent human-bovine, Indian neonatal strains

China RV Disease Burden

- 6 sentinel hospitals
- n= 3149
- RV+ rate 50%

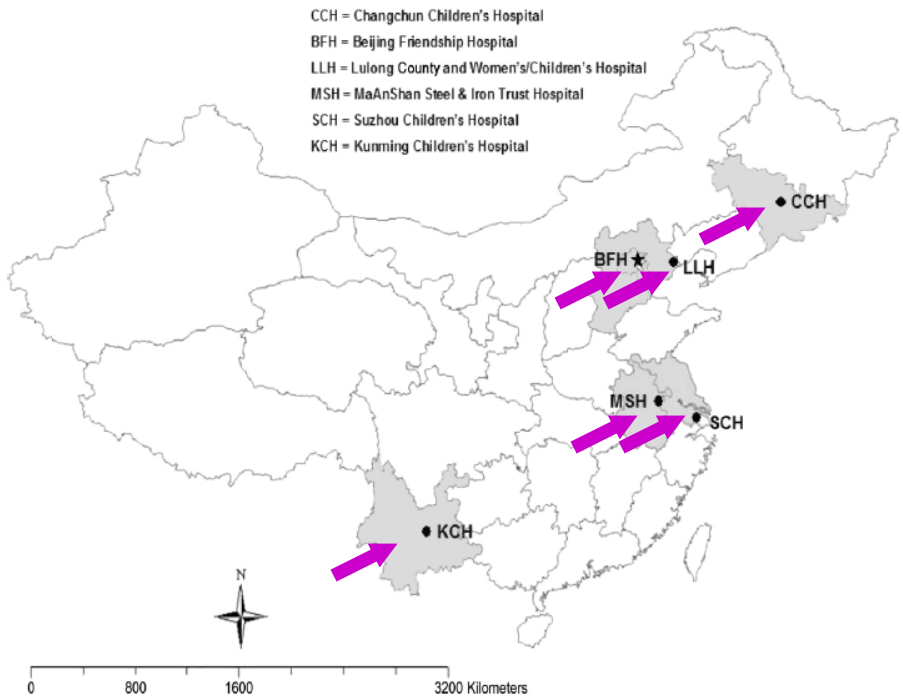


Figure 1. Locations of the 6 sentinel hospitals for rotavirus surveillance, People's Republic of China, 1 August 2001–31 July 2003

Fang ZY et al. JID. 2005;192:S94-99

Hong Kong RV disease burden

- RV+ rate = 30%
- Incidence of hospitalisation for RV
  - 8.8 per 1000 children < 5yrs
- 4x previous "passive" estimate

1 in 24

cumulative risk of hospitalisation for RV by age 5 years

Nelson et al. JID. 2005;192:S71-79

India RV disease burden

- Passive surveillance study
- 6 hospitals (~65% admissions)
- RV+ rate = 24%

- Incidence of hospitalisation for RV
- 3.4 per 1000 children < 5yrs

Bahl R et al. JID. 2005;192:S114-119

Japan RV disease burden

- 3 sentinel hospitals (n=443)
- RV+ rate = 58%
- Incidence of hospitalisation for RV
- ~ 15 per 1000 children < 5yrs

1 in 15

cumulative risk of hospitalisation for RV by age 5 years

Nakagomi T et al. JID. 2005;192:S106-110

Korea RV disease burden

- RV+ rate (4106 children)
  - INPATIENTS = 73%
  - OUTPATIENTS = 18%
- Incidence of hospitalisation for RV:

  11.6 per 1000 children < 5yrs
- Overall incidence of RV:

  57 per 1000 children < 5yrs

Kim et al. JID. 2005;192:S49-56

Malaysia RV disease burden

- Ministry of Health Data
- ~14,000 GE admissions
- RV+ rate for hospitalised RV = 50%

1 in 61

cumulative risk of hospitalisation for RV by age 5 years

Hsu et al. JID. 2005;192:S80-86

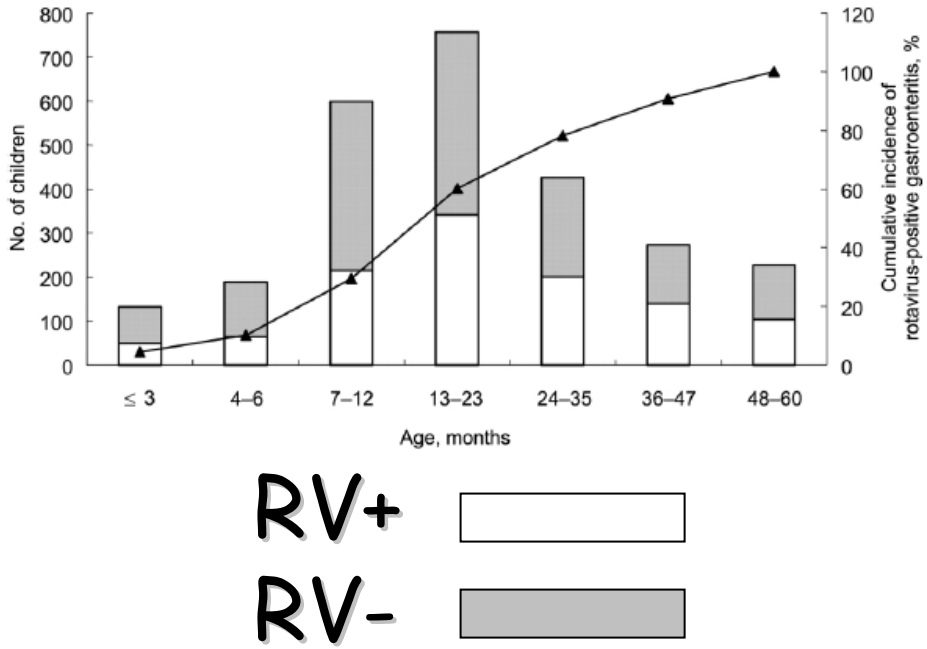
Myanmar RV disease burden

- Diarrhea 18% of hospitalisations
- n=1736
- RV+ rate = 53%

Moe K et al. JID. 2005;192:S111-113

Taiwan RV disease burden

- Enrolled 2600
- RV+ rate 43%
- Bacteria 11%
- Adenovirus 2.5%
- RV + other 3.9%



Chen et al. JID. 2005;192:S44-48

Thailand RV disease burden

- Enrolled 4057
- RV+ rate 43%
- Community RV+ rate 12%

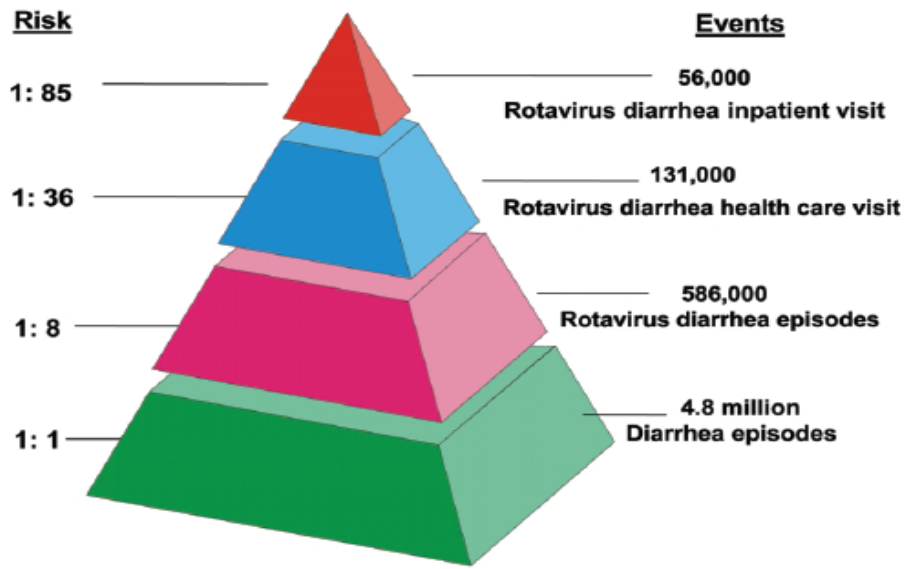
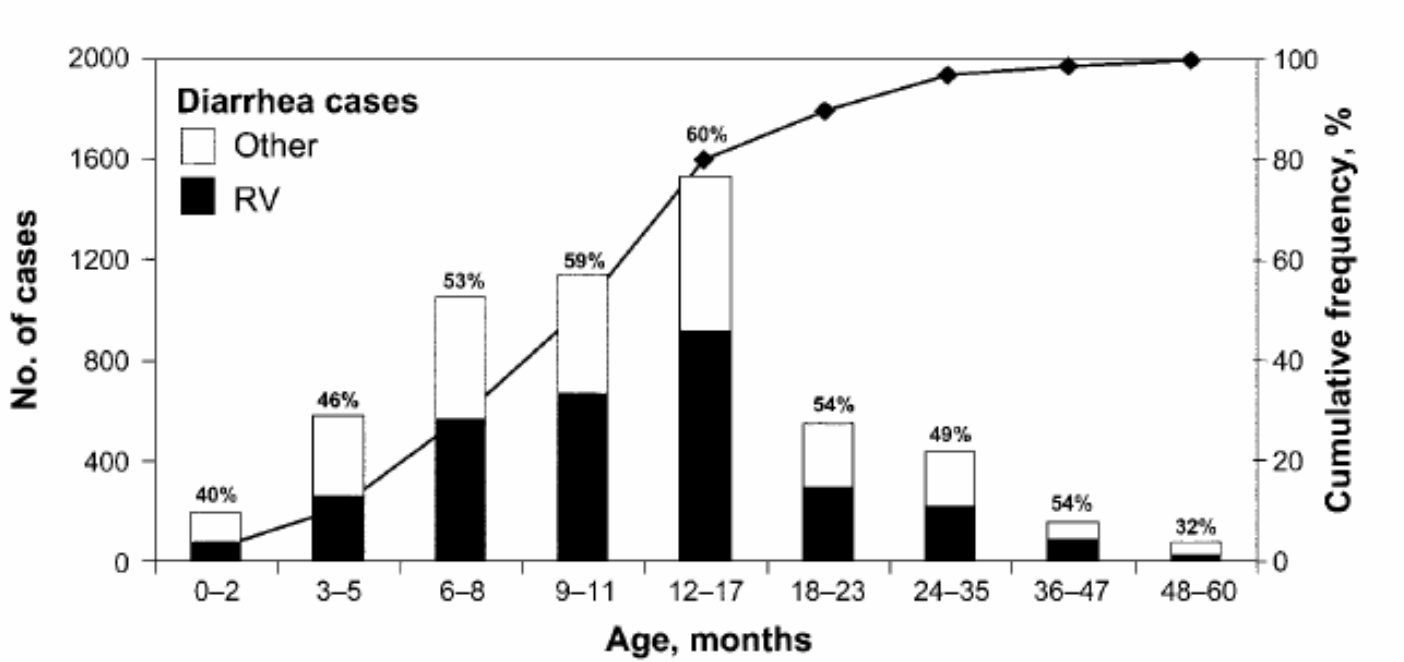


Figure 3. Summary of disease burden associated with rotavirus infection in Thailand

Jiraphongsa et al. JID. 2005;192:S87-93

Vietnam RV disease burden

- n=5809 (2000-2003)
- RV+ rate = 55%



Nguyen Van Man et al. JID. 2005;192:S127-132

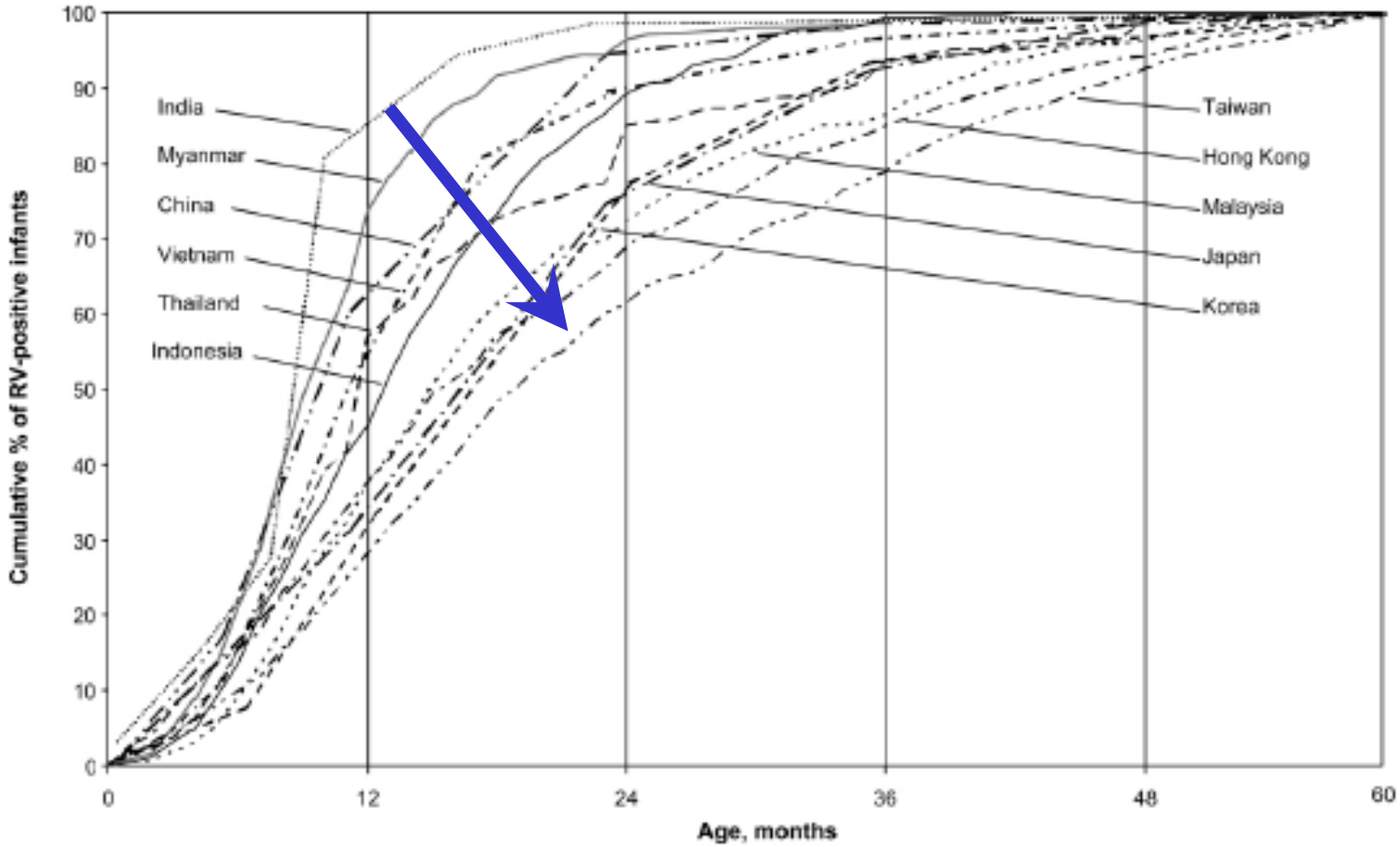
Asian Rotavirus Disease Burden

Sites	% RV+
Korea	73 (180/249)
Japan	58 (256/443)
Vietnam	55 (3195/5809)
Myanmar	53 (920/1736)
China	50 (1590/3149)
Taiwan	47 (1118/2600)
Thailand	43 (1745/4057)
Hong Kong	30 (1760/5881)

45% ALL DIARRHOEA ADMISSION RV+

Data from JID. 2005;192:

Variation in peak age of onset



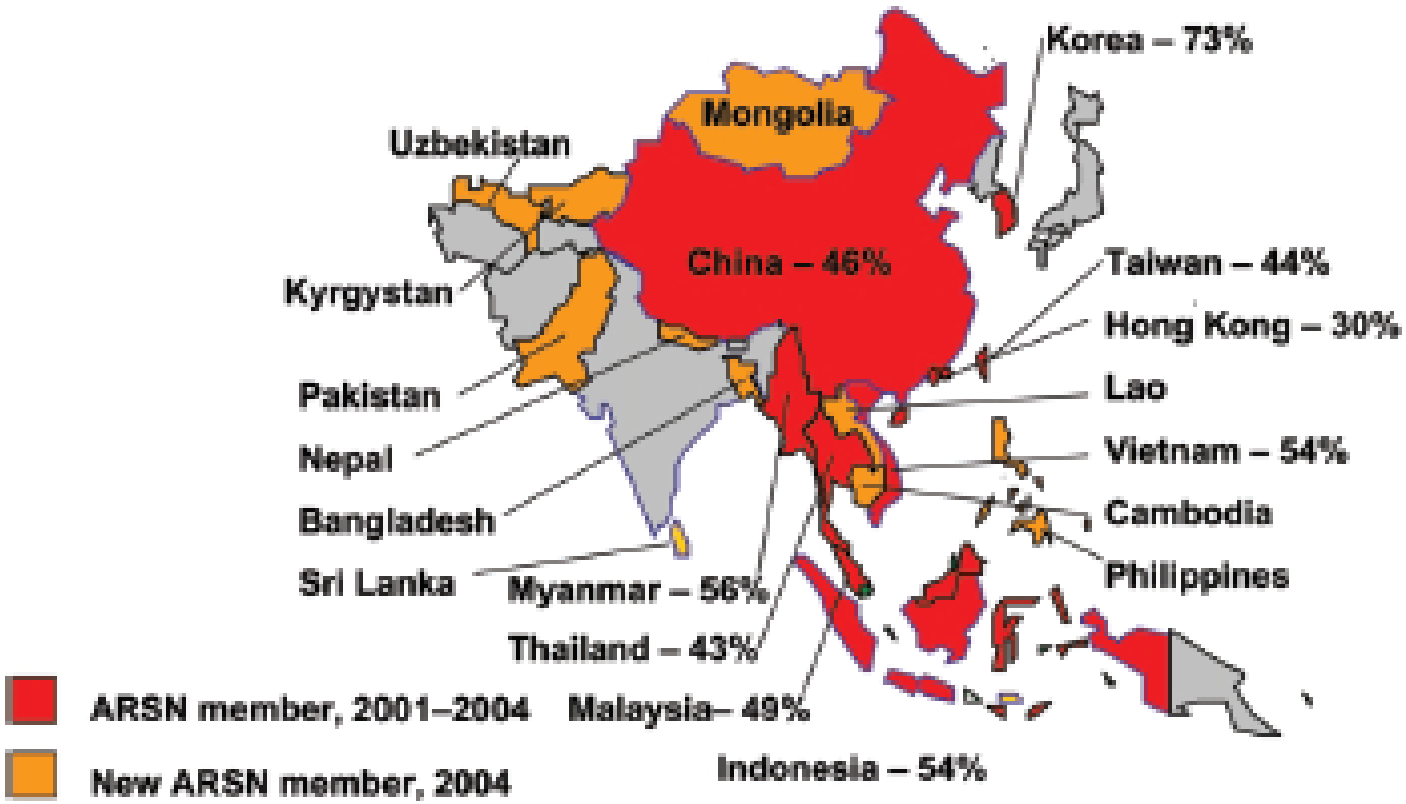
GDP/capita

Asian Rotavirus Serotypes (%)

Sites	*n*	G1	G2	G3	G4	G9	M/O/U
China	470	14	5	67	<1	5	10
Hong Kong	300	49	15	23	4	5	5
India	137	23	13	6	-	15	42
Korea	203	25	13	19	2	39	2
Taiwan	300	31	10	9	4	37	9
Thailand	838	1	17	<1	5	55	22
Vietnam	499	47	15	-	10	22	6

Data from JID. 2005;192:

Asian RV Disease Burden



"Higher than anticipated"

Japan Economic Burden of rotavirus-associated admissions

- Direct medical cost USD 1236
- Extrapolated total direct medical cost USD 96 M

Nakagomi T et al. JID. 2005;192:S106-110

Cost estimations for Hong Kong

- Total social cost USD 4.3 M
- Total direct medical cost USD 4 M
- 4 x higher than previous estimate

- Government cost ~ USD 1800
- Family cost USD 120

Nelson et al. JID. 2005;192:S64-70

Projected Cost-Effectiveness of Rotavirus Vaccination for Children in Asia

Laura Jean Podewils,[1] Lynn Antil,[2] Erik Hummelman,[1] Joseph Bresee,[1] Umesh D. Parashar,[1] and Richard Rheingans[2]

[1]Respiratory and Enteric Viruses Branch, Division of Viral and Rickettsial Diseases, National Center for Infectious Diseases, Centers for Disease Control and Prevention, and [2]Department of International Health, Rollins School of Public Health, Emory University, Atlanta, Georgia

Background. New rotavirus vaccines may soon be licensed, and decisions regarding implementation of their use will likely be based on the health and economic benefits of vaccination.

Methods. We estimated the benefits and cost-effectiveness of rotavirus vaccination in Asia by using published estimates of rotavirus disease incidence, health care expenditures, vaccine coverage rates, and vaccine efficacy.

Results. Without a rotavirus vaccination program, it is estimated that 171,000 Asian children will die of rotavirus diarrhea, 1.9 million will be hospitalized, and 13.5 million will require an outpatient visit by the time the Asian birth cohort reaches 5 years of age. The medical costs associated with these events are approximately $191 million; however, the total burden would be higher with the inclusion of such societal costs as lost productivity. A universal rotavirus vaccination program could avert approximately 109,000 deaths, 1.4 million hospitalizations, and 7.7 million outpatient visits among these children.

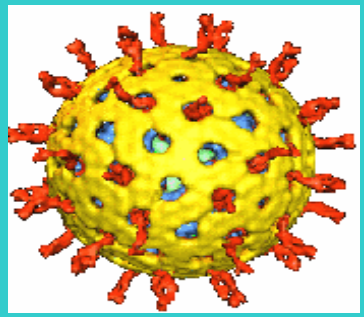
Conclusions. A rotavirus vaccine could be cost-effective, depending on the income level of the country, the price of the vaccine, and the cost-effectiveness standard that is used. Decisions regarding implementation of vaccine use should be based not only on whether the intervention provides a cost savings but, also, on the value of preventing rotavirus disease–associated morbidity and mortality, particularly in countries with a low income level (according to 2004 World Bank criteria for the classification of countries into income groups on the basis of per capita gross national income) where the disease burden is great.

Projected cost-effectiveness RV vaccines in Asia

- In Asia by 5 years of age
  - 171,000 will die (109,000)*
  - 1.9 M hospitalisations (1.4M)*
  - 13.5 M outpatient visits (7.7M)*
- Medical cost $191 M
- Cost-effectiveness will depend on income level, vaccine price & standard used

* Potentially averted by universal vaccination

Podewils L et al. JID. 2005;192:S133-145



ASIAN
ROTAVIRUS
SURVEILLANC
ENETWORK

5th ARSN Meeting Jul 2006

Sites	% RV+
Bangladesh	33
Cambodia	51
China	49
Indonesia	53
Kyrgyzstan	24
Lao	57
Mongolia	39

Sites	% RV+
Myanmar	56
Nepal	49
Pakistan	36
Sri Lanka	24
Thailand	44
Philippines	38
Uzbekistan	33

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 5, 2006 VOL. 354 NO. 1

Safety and Efficacy of an Attenuated Vaccine against Severe Rotavirus Gastroenteritis

Guillermo M. Ruiz-Palacios, M.D., Irene Pérez-Schael, M.Sc., F. Raúl Velázquez, M.D., Hector Abate, M.D., Thomas Breuer, M.D., SueAnn Costa Clemens, M.D., Brigitte Cheuvart, Ph.D., Felix Espinoza, M.D., Paul Gillard, M.D., Bruce L. Innis, M.D., Yolanda Cervantes, M.D., Alexandre C. Linhares, M.D., Pío López, M.D., Mercedes Macías-Parra, M.D., Eduardo Ortega-Barría, M.D., Vesta Richardson, M.D., Doris Maribel Rivera-Medina, M.D., Luis Rivera, M.D., Belén Salinas, M.D., Noris Pavía-Ruz, M.D., Jorge Salmerón, M.D., Ricardo Rüttimann, M.D., Juan Carlos Tinoco, M.D., Pilar Rubio, M.D., Ernesto Nuñez, M.D., M. Lourdes Guerrero, M.D., Juan Pablo Yarzábal, M.D., Silvia Damaso, M.Sc., Nadia Tornieporth, M.D., Xavier Sáez-Llorens, M.D., Rodrigo F. Vergara, M.D., Timo Vesikari, M.D., Alain Bouckenooghe, M.D., Ralf Clemens, M.D., Ph.D., Béatrice De Vos, M.D., and Miguel O'Ryan, M.D., for the Human Rotavirus Vaccine Study Group*

ORIGINAL ARTICLE

Safety and Efficacy of a Pentavalent Human–Bovine (WC3) Reassortant Rotavirus Vaccine

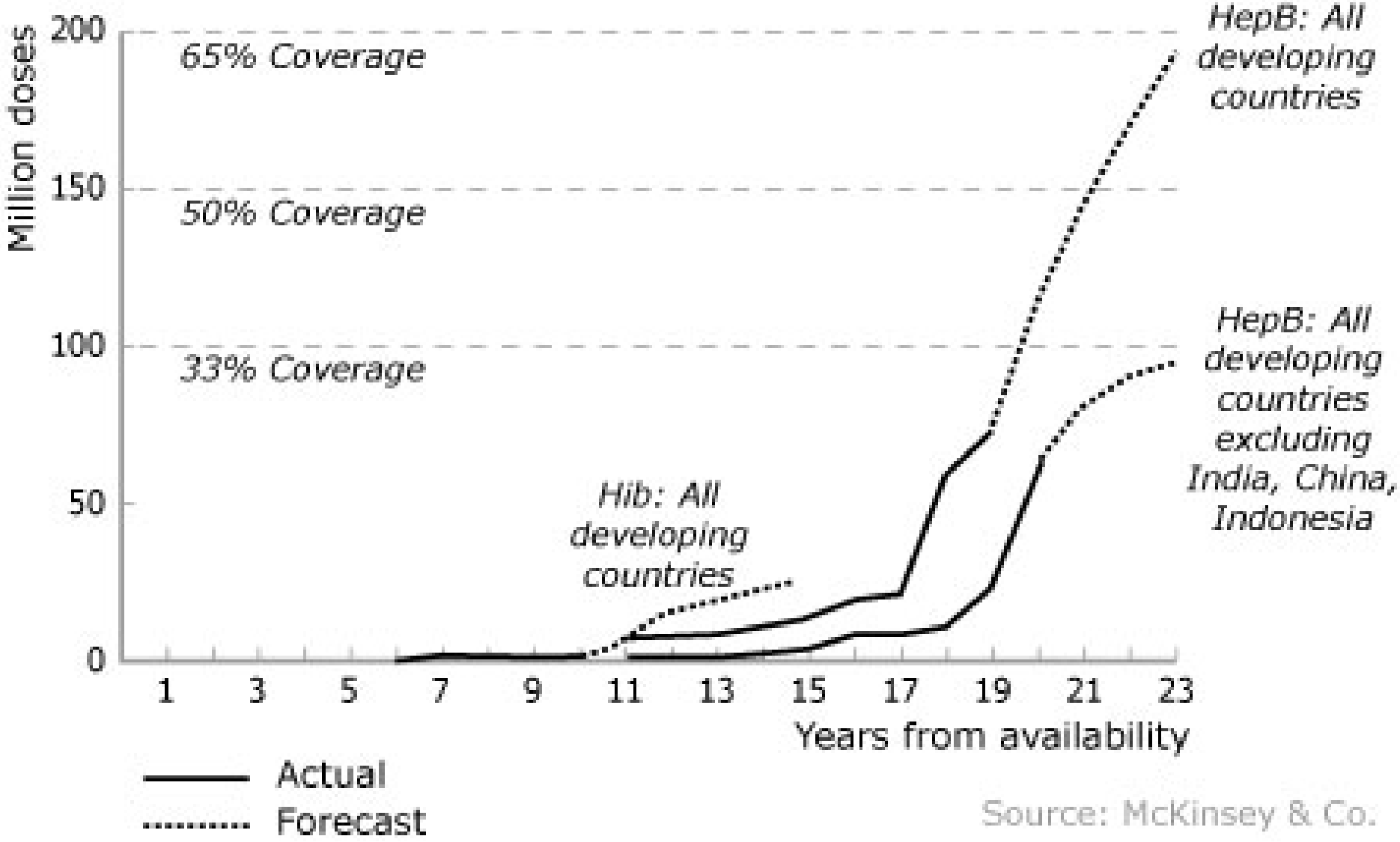
Timo Vesikari, M.D., David O. Matson, M.D., Ph.D., Penelope Dennehy, M.D., Pierre Van Damme, M.D., Ph.D., Mathuram Santosham, M.D., M.P.H., Zoe Rodriguez, M.D., Michael J. Dallas, Ph.D., Joseph F. Heyse, Ph.D., Michelle G. Goveia, M.D., M.P.H., Steven B. Black, M.D., Henry R. Shinefield, M.D., Celia D.C. Christie, M.D., M.P.H., Samuli Ylitalo, M.D., Robbin F. Itzler, Ph.D., Michele L. Coia, B.A., Matthew T. Onorato, B.S., Ben A. Adeyi, M.P.H., Gary S. Marshall, M.D., Leif Gothefors, M.D., Dirk Campens, M.D., Aino Karvonen, M.D., James P. Watt, M.D., M.P.H., Katherine L. O'Brien, M.D., M.P.H., Mark J. DiNubile, M.D., H Fred Clark, D.V.M., Ph.D., John W. Boslego, M.D., Paul A. Offit, M.D., and Penny M. Heaton, M.D., for the Rotavirus Efficacy and Safety Trial (REST) Study Team

Newly licensed Vaccines

- Safety & efficacy demonstrated in high and middle income countries
- Some data on use with OPV
- Possible effects of breast milk
- Studies underway in Bangladesh & South Africa

Prospects for the early introduction of rotavirus vaccines into universal programs in Asian countries?

Historical Perspective: Introducing Vaccines into Developing Countries



Source: McKinsey & Co.

ROTAVIRUS VACCINE PROGRAM

A PATH AFFILIATE

- Initial US$30 Million over three years
- A new paradigm for vaccine development ?
- Aims to ***fast-track*** development & introduction of rotavirus vaccines in developing countries

GAVI
THE GLOBAL ALLIANCE FOR VACCINES & IMMUNIZATION

TheVaccineFund
Every child. Every where.

CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

Declaration

by Representatives of Ministries of Health in the Americas‡

Sixth International Rotavirus Symposium

Mexico City, Mexico

July 7–9, 2004

‡ *Argentina, Bolivia, Brazil, Ecuador, Guatemala, Honduras, Jamaica, Mexico, Nicaragua, Panama, Peru, Paraguay, Saint Vincent, Surname, Trinidad and Tobago, and Venezuela.*

- To call upon PAHO and its Revolving Fund for the acquisition of vaccines to work together with bilateral and multilateral agencies, the Global Alliance for Vaccines and Immunization and the manufacturers of vaccines to facilitate the introduction of the rotavirus vaccine, as soon as it becomes available at affordable price for the countries in the region.

Countries using RV vaccine for universal immunization

- United States - ACIP recommendation
- Brazil - since March 2006
- Panama
- Venezuela
- (Austria)
- (Mexico)

Human Development Reports

HDI rank		GDP per capita (PPP US$) 2003
High Human Development		
10	United States	37,562
11	Japan	27,967
17	Austria	30,094
22	Hong Kong, China (SAR)	27,179
28	Korea, Rep. of	17,971
53	Mexico	9,168
56	Panama	6,854
Medium Human Development		
61	Malaysia	9,512
63	Brazil	7,790
73	Thailand	7,595
75	Venezuela	4,919
84	Philippines	4,321
85	China	5,003a
93	Sri Lanka	3,778
109	Kyrgyzstan	1,751
110	Indonesia	3,361
111	Uzbekistan	1,744
129	Myanmar	..
130	Cambodia	2,078b
133	Lao People's Dem. Rep.	1,759
135	Pakistan	2,097
136	Nepal	1,420
139	Bangladesh	1,770

Notes:

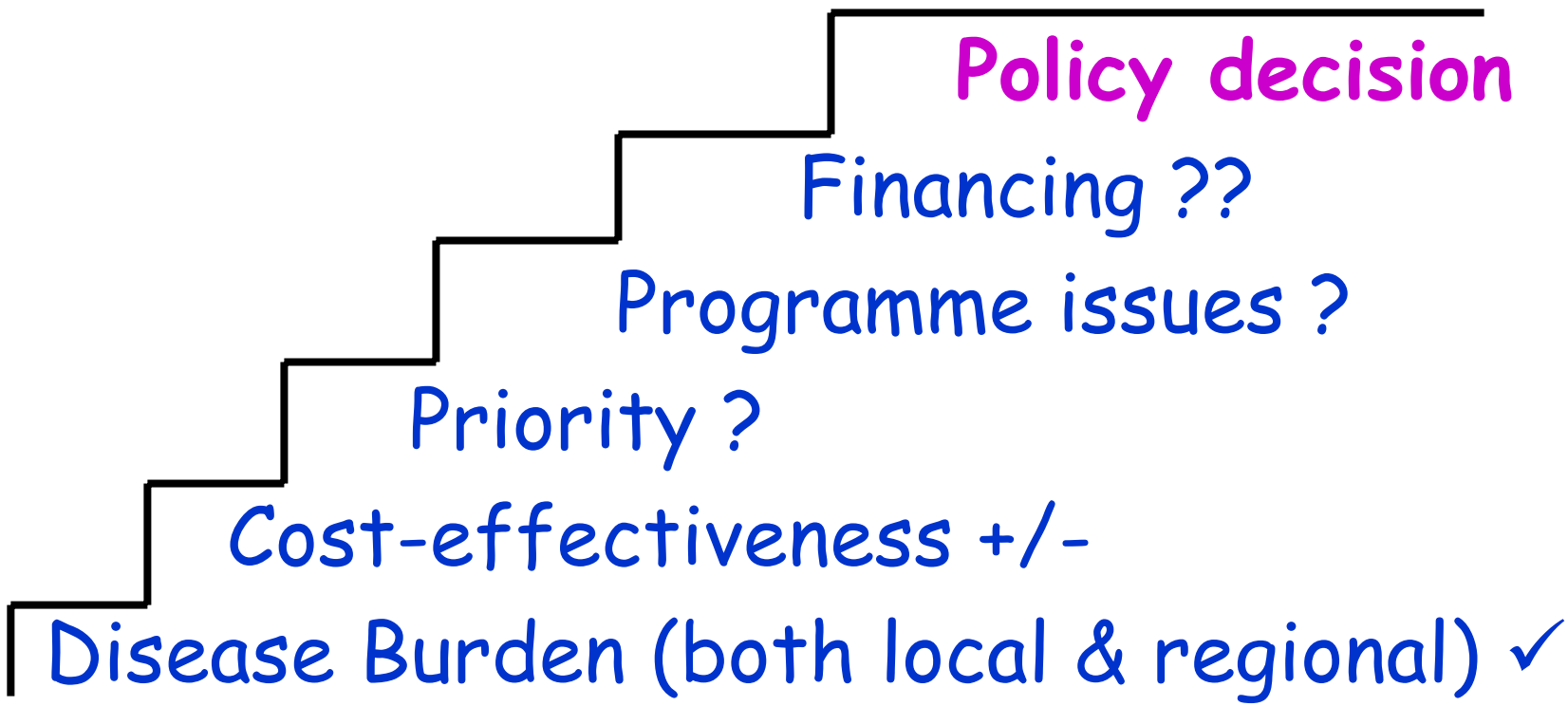
a. Estimate based on a bilateral comparison between China and the United States (Ruoen, Ren and Chen Kai. 1995. "China's GDP in US Dollars Based on Purchasing Power Parity." World Bank Policy Research Working Paper No. Washington, D.C.).

b. Estimates are based on regression.

Source:

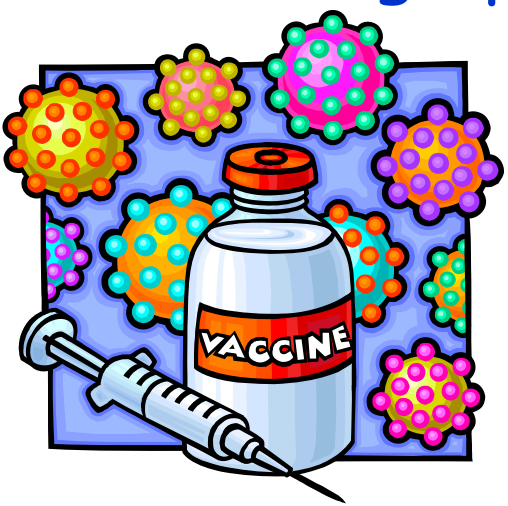
Column 1: calculated on the basis of GDP and population data from World Bank. 2005. World Development Indicators 2005. CD-ROM. Washington, DC.; aggregates calculated for the Human Development Report Office by the Wo

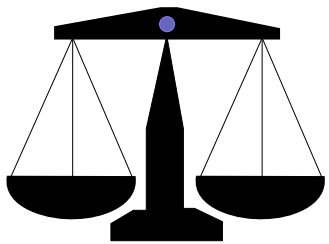
Steps in decision making process?



Will rotavirus vaccines be "affordable"?

- What is seen as a "priority" for governments will largely determine "affordability"
  - Vaccines may be cost-effective but if a low priority = "NOT affordable"
  - Other high cost items may be considered a high priority = "Affordable"





The introduction of new vaccines into developing countries II. Vaccine financing

- Proposal: "Vaccine Procurement Baseline"
- Set at a minimum of 0.01% of GNP,
  - i.e. the amount of money that individual countries should devote to it's own vaccine procurement
  - "Global Funds" would pick up the difference

Mahoney et al. Vaccine 2000;18:2625-35

How much do countries spend on vaccines ?

- Poor developing countries spend ~ 0.13% GNP on basic EPI vaccines
- US spends ~ 0.035% of GNP on EPI + several "new" vaccines
- UK spends ~ 0.013% GNP
- Canada spends ~ 0.0175% GNP

Mahoney et al. Vaccine 2000;18:2625-35

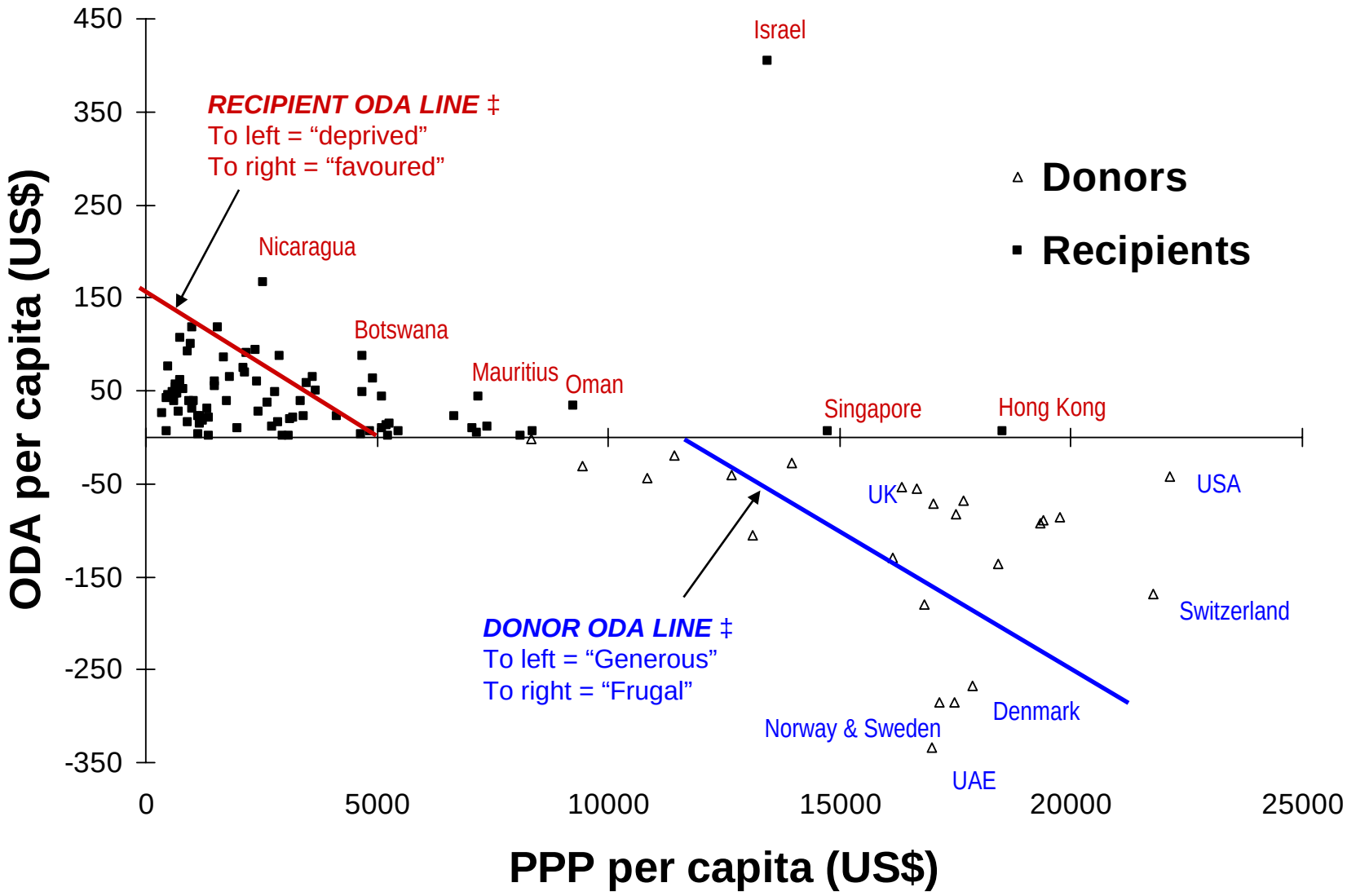
Definition of Official Development Assistance

- Undertaken by official sector
- Given to developing countries
- Promote economic development & welfare
- Concessional (grant element of >25%)

The Rich Man's Club 1991

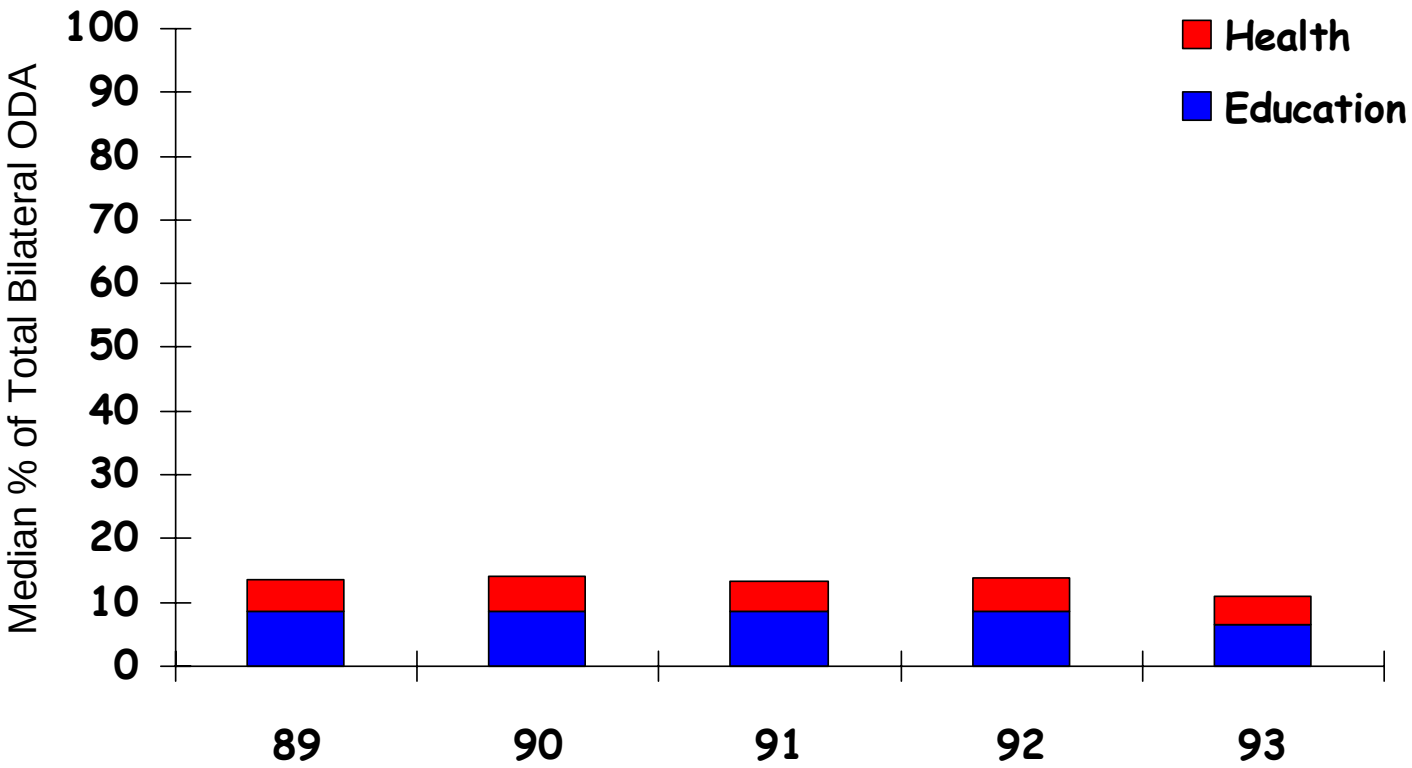
	PPP$/cap	$/cap (given)	+received
United States	22130	(42)	Richest nation
Switzerland	21780	(168)	
Germany	19770	(87)	
Japan	19390	(89)	
Canada	19320	(92)	
Hong Kong	18520	+6	Richest recipient of ODA
France	18430	(137)	
Denmark	17880	(268)	
Austria	17690	(68)	
Belgium	17510	(83)	
Sweden	17490	(285)	
Norway	17170	(285)	
Italy	17040	(71)	
UAE	17000	(332)	Most generous
Netherlands	16820	(180)	
Australia	16680	(55)	
United Kingdom	16340	(54)	
Finland	16130	(129)	
Singapore	14734	+7	
New Zealand	13970	(28)	Most frugal
Israel	13460	+405	Recipient of most ODA
Kuwait	13126	(105)	

UNDP 1994



Nelson & Yu. Lancet 1996;346:1642-3

British ODA for Health & Education



Nelson & Yu. Lancet 1996;346:1642-3

British Aid 1989-93

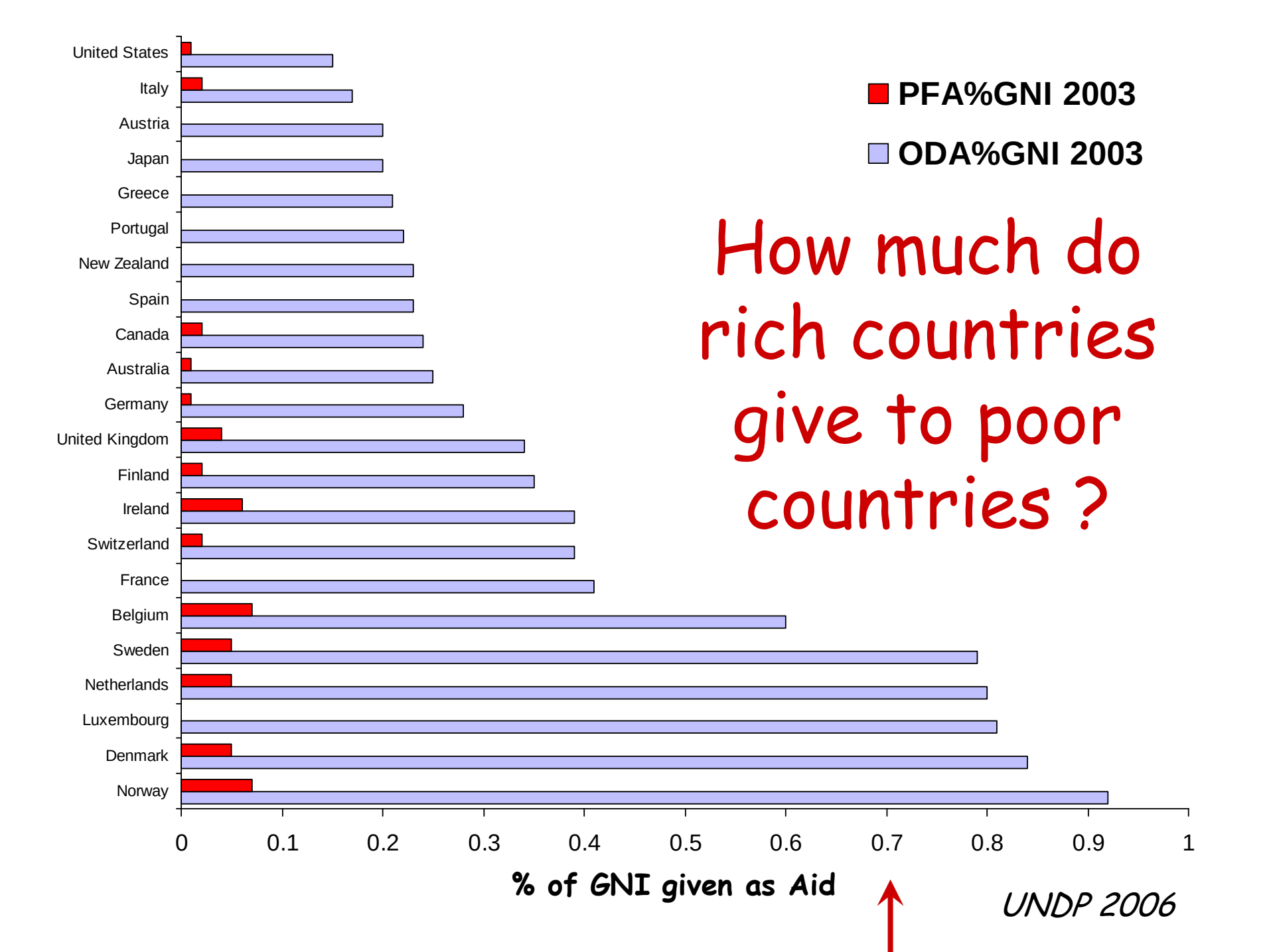
UN Aid Target (% of GNP):	0.7%
British Aid actually given:	0.3%
Least developed countries:	0.1%
Aid to social programmes:	0.01%
Aid to 1° and 2° education:	0.002%

Nelson & Yu. Lancet 1996;346:1642-3

Poverty Focused Assistance : new category of development aid

"Concessional aid (100% grant element) that is provided by the official sector and spent within the world's Least Developed Countries to promote social development"

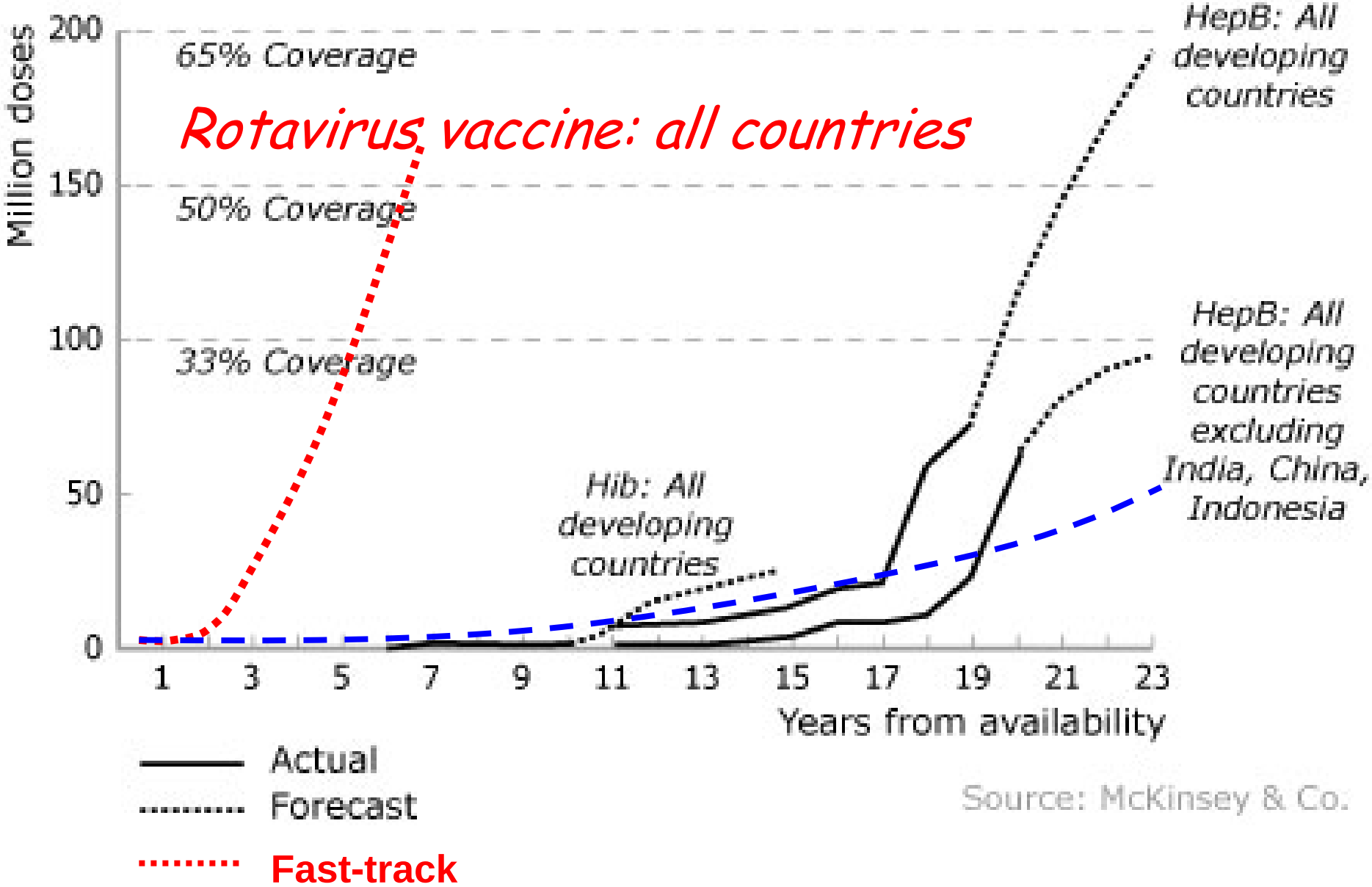
Nelson & Yu. Lancet 1996;346:1642-3


PFA%GNI 2003
ODA%GNI 2003
How much do rich countries give to poor countries ?
United States
Italy
Austria
Japan
Greece
Portugal
New Zealand
Spain
Canada
Australia
Germany
United Kingdom
Finland
Ireland
Switzerland
France
Belgium
Sweden
Netherlands
Luxembourg
Denmark
Norway
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
% of GNI given as Aid
UNDP 2006

Summary

- Significant RV disease burden in Asia
- RV vaccines likely to be cost-effective in many high & middle income countries
- Preliminary data on disease burden from poorer countries
- However data on vaccine efficacy needed from poorer countries, including data on OPV & breastfeeding

Historical Perspective:
Introducing Vaccines into Developing Countries



Source: McKinsey & Co.

Thank you